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DTU Environment
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PhD Thesis
March 2010

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Preface

The aim of this PhD thesis is to present the progress in modeling the environmental exposure of ionizable chemicals based on the research undertaken from March 2007 to February 2010 at the Department of Environmental Engineering of the Technical University of Denmark, under the supervision of Dr. Stefan Trapp.

The thesis is a contextualized summary of six scientific papers covering all major findings of the PhD project, except for chapter 5.4, which refers to two unpublished project reports. The six scientific papers (one commentary and five research articles) are included as appendices to this thesis.

I. Franco A, Ferranti A, Davidsen C, Trapp S. 2010. An unexpected challenge: ionizable compounds in the REACH chemical space. *Int J LCA* (commentary, in print).

II. Franco A, Trapp S. 2008. Estimation of the soil-water partition coefficient normalized to organic carbon for ionizable organic chemicals. *Environ Toxicol Chem 27*: 1995-2004.

III. Franco A, Fu W, Trapp S. 2009. Influence of soil pH on the sorption of ionizable chemicals: modeling advances. *Environ Toxicol Chem* 28: 438-464.

IV. Fu W, Franco A, Trapp S. 2009. Methods for estimating the bioconcentration factor of organic electrolytes. *Environ Toxicol Chem* 28: 1372-1379.

V. Trapp S, Franco A, Mackay D. 2010. Multi-media partitioning of ionizing organics: finding activity feasible (manuscript draft).

VI. Franco A, Trapp S. 2010. A multimedia activity model for ionizable compounds: validation study with 2,4-dichlorophenoxyacetic acid, aniline and trimethoprim. *Environ Toxicol Chem* 29. (DOI: 10.1002/ect.115, in print).

The papers are not included in this www-version but can be obtained from the library at DTU Environment. Contact info: Library, Department of Environmental Engineering, Technical University of Denmark, Miljoevej, Building 113, DK-2800 Kgs. Lyngby, Denmark or library@env.dtu.dk.

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Kgs. Lyngby, Antonio Franco
January 2010

Summary

The modern society benefits from the use of chemicals but some of them may be harmful. To protect humans and the environment, it is necessary to early identify potential adverse effects and adequately manage the risks. In Europe, the EU regulation on the Registration, Evaluation, Authorization, and restriction of CHemicals (REACH) urged the scientific community to improve existing tools to predict the risks associated with the exposure of humans and the environment to chemicals. The evaluation of chemicals (risk assessment) combines (eco)toxicological information (effect assessment) with the predicted exposure to a given substance (exposure assessment). It was estimated that 30 000 chemicals, most of which organic chemicals, need to be risk assessed under REACH before 2018.

Environmental fate models have been increasingly used for exposure assessment. These models predict concentrations of chemicals emitted into the environment in the different compartments (air, water, soil and sediments) from the physicochemical properties and the degradation rates of the substance. Currently used exposure models, as described in the EU Technical Guidance Documents (TGD), were developed for neutral chemicals and rely on assumptions and algorithms that are valid for neutral molecules, but not necessarily for ionizable compounds.

Many pesticides, most pharmaceuticals and about 50% of REACH chemicals are ionizable. Two characteristics influence the behaviour of ionizable chemicals in the environment and differentiate them from neutral chemicals: the simultaneous occurrence of two or more species and the electric charge of ions. The objective of this PhD project was to improve environmental exposure models for ionizable organic chemicals by addressing these two challenges. First, new equations were developed to estimate key environmental partition coefficients of organic ionics: the solid-water partition coefficient (K_d) and the bioconcentration factor (*BCF*). Second, a new system of chemodynamics, based on the activity was derived. The new algorihms were integrated in a regional multimedia environnmental exposure model using the activity approach. Finally, the model was tested and compared to existing ones.

The solid water distribution coefficient (K_d) is a key parameter for mobility and fate of organic pollutants. While the K_d of neutral organic chemicals is governed by lipophilicity, ions are also attracted or repulsed by electrical charges. Lipophilicity is well described by the octanol-water partition coefficient (K_{OW}); electrical interactions depend on the valency and on the electrical properties of the solvent or sorbent. The fractions of ionic species are calculated by the *Henderson-Hasselbalch equation* from the pH and the negative decadic logarithm of the dissociation constant (pK_a). By applying a species-specific sorption model, regressions were developed to estimate the soil-water partition coefficient normalized to organic carbon (K_{OC}) from the K_{OW} of the neutral molecule and the pK_a. The regressions were calibrated and tested on independent

experimental datasets. The new regressions proved more accurate than the ones suggested in the EU TGD. No predictive method specifically had been developed so far for bases and amphoters. The mean error of the new equations was estimated at approximately 0.5 log K_{OC} units. A major reason for uncertainty in the model predictions is the variability of soil pH, which influences speciation equilibria as well as the soil surface chemistry. Sorption of organic acids is greater at lower pH. Probably due to the local acidity near the organic colloid-water interface, the optimal pH to model dissociation was found on average 0.6 pH units lower than the bulk soil pH. The knowledge of the soil pH allows calculating the fractions of neutral and ionic species in the system, thus improving the regression for acids. The same approach was not successful for bases because of the contrasting impact of pH on the total sorption.

The bioaccumulation potential is an important criterion in chemicals risk assessment. The bioaccumulation of neutral compounds depends mainly on lipophilicity, whereas dissociation, the pH-dependent ion trap, and electrical attraction of cations impact the *BCF* of ions. Existing methods and new regressions for estimating the *BCF* of ionizable chemicals were tested. The regression suggested in the TGD performed best when the log K_{OW} calculated at a given pH (log *D*) is used as predictor. New species-specific regressions based on K_{OW} and pK_a performed similarly, with mean errors of approximately 0.4 on log *BCF*. A dynamic cell model based on the Fick-Nernst-Plank equation gave accurate predictions for bases but not for acids.

A new system of equations based on chemical activity (activity approach) was developed to describe partitioning and transport of ionizable compounds. The activity approach provides the thermodynamically exact equations to describe the behaviour of neutral and ionic molecules in non-ideal systems. The total concentration in a phase or a bulk compartment is the product of the total activity and the activity capacity, the capacity of a phase or compartment to absorb a compound. The activity approach is a useful complement of the well known fugacity approach.

Based on this approach, a Multimedia Activity Model for Ionics (MAMI) was developed and tested. MAMI features pH- and ionic strength dependency and includes species-specific estimations of partition coefficients. A validation study with selected chemicals on a regional scale emission scenario showed the impact of dissociation, electrical interactions with solids, humidity in air and, to a lesser extent, of salinity in seawater on the predicted environmental concentrations of organic ionics. The performance of MAMI compared to a conventional fugacity model indicates that the activity approach can enlarge the applicability domain and improve the predictions of multimedia exposure models. The sensitivity and uncertainty analysis of MAMI highlighted that the pH and the pK_a, describing ionization, are among the most sensitive model parameters and should be included in probabilistic exposure assessments.

Dansk sammenfatning

Det moderne samfund afhænger af anvendelsen af kemiske stoffer, men nogle stoffer kan være skadelige for mennesker og miljø. En tidlig identificering af potentielle skadelige virkninger på mennesker og miljøet er nødvendig for at behandle risici og sikre et højt beskyttelseniveau.

EU's regulering om registrering, vurdering og godkendelse af kemikalier (REACH) tilskyndede videnskabsfolk til at udvikle og forbedre nuværende risikovurderingsmetoder. Disse metoder estimerer den potentielle eksponering for kemiske stoffer af menneske og miljø. Evaluering af kemikalier (risikovurdering) kombinerer (øko)toksikologiske data (effektvurdering) samt den estimerede eksponering af mennesker og miljø for et stof (ekponeringsvurdering). Omkring 30 000 kemikalier, mestendels organiske stoffer, skal risikovurderes inden 2020.

Multimedie eksponeringsmodeller har været almindeligt anvendt i ekponeringsvurderingen af kemikalier i miljøet. Disse modeller forudsiger koncentrationer i forskellige dele af miljøet (luft, vand, jord og sedimenter) ud fra fysisk-kemiske egenskaber og nedbrydningshastigheder af kemikalier. De pt anvendte eksponeringsmodeller, såsom beskrevet i EU's tekniske vejledningsdokumenter (TGD) blev udviklet for neutrale kemikalier og anvender antagelser og algoritmer der kun er gyldige for neutrale molekyler, ikke for ioner.

Mange pesticider, de fleste lægemidler og omkring 50% af REACH kemikalierne gennemgår ionisering i miljøet. To egenskaper påvirker ioniserbare kemikaliers miljømæssige skæbne og adskiller dem fra neutrale molekyler: 1) den samtidige forekomst af to eller flere kemiske species og 2) ionernes ladning. Formålet med dette PhD projekt var at tage fat på disse to udfordringer for at forbedre miljømæssige ekponeringsmodeller for ioniserbare organiske stoffer. Først blev nye regressionsligninger oprettet til estimering af vigtige miljømæssige fordelingskoefficienter for ioniserbare kemikalier: jord-vand fordelingskoefficienten (K_d) og biokoncentrationsfaktoren (BCF). Disse algoritmer blev integreret i en regional multimedie miljømæssige ekponeringsmodel baseret på "aktivitets metoden". Til sidst blev modellen testet og sammenlignet med gældende modeller.

Jord-vand fordelingskoefficienten er en nøgle-parameter for mobilitet og skæbne af organiske forurenende stoffer. Mens K_d for neutrale kemikalier afhænger af lipophilicitet, gennemgår ioner tiltrænings- og frastødningskraft. Lipophilicitet beregnes fra oktanol-vand fordelingskoefficienten (K_{OW}); ionisering beregnes med Hendersson-Hasselbalch ligningen ud fra dissociationskonstanten (pK_a). Ved anvendelse af en species specifik model blev regressioner udviklet til estimering af jord-vand fordelingskoefficienten normaliseret til organisk kulstof (K_{OC}) ud fra det neutrale molekyles K_{OW} og pK_a. Regressioner blev kalibreret og testet ved brug af et uafhængigt eksperimentelt datasæt. Den ny regression for syrer viste sig at være nøjagtigere end den

der foreslåes i EU's TGD. Hidtil var der ingen andre gældende metoder særligt oprettet til baser og amfotere kemikalier. De nye regressioners gennemsnitlige fejl beregnedes til omkring 0.5 på en log scala.

Variationen i jordens pH, som påvirker ionernes dissociering såvel som kolloidernes overfladekemi, bidrager til usikkerheden af de beregnede koefficienter. Sandsynligvis på grund af den lavere pH tæt på overfladen af negativt ladede ler- eller humus-kolloider, er den optimale pH til dissocieringsmodellering (for syre) gennemsnitligt 0.6 pH enheder lavere end den samlede jordvandspH. Viden om jordens pH muliggør beregninger af ioners og neutrale molekylers koncentrationer i systemet. På den måde blev regressionen for organiske syrer forbedret. Det samme forsøg mislykkedes for baser fordi pH har modsatrettede indvirkninger på basers sorption.

Potentialet for bioakkumulering (*BCF*) er et vigtigt kriterie i kemikaliers risikovurdering. Bioakkumulering af neutrale stoffer afhænger hovedsagelig af lipophilicitet, hvorimod dissociering, den pH-afhængige ion fælde samt den elektriske tiltrækning af kationer påvirker ionernes evne til bioakkumulering. Gældende metoder og nye regressioner til beregning af *BCF* for ioniserbare kemikalier blev testet. Den foreslåede ligning i TGD var bedst når oktanol-vand fordelingskoefficient beregnet ved en bestemt pH værdi (log *D*) blev anvendt i stedet for det neutrale molekyles log K_{OW}. Nye species specifikke regressioner baseret på K_{OW} og pK_a viste lignende opførsel, med en gennemsnitlig fejl på 0.4 log enheder for *BCF*. En dynamisk celle model baseret på Fick-Nernst-Plank ligningen kunne beregne nøjagtige værdier for baser men ikke for syrer.

Et nyt sæt formler baseret på den kemiske aktivitet (aktivitets metode) blev opstillet til bestemmelse af fordeling og transport af ioniserbare stoffer. Denne metode angiver de rigtige termodynamiske ligninger til beskrivelse af neutrale og ioniserbare molekylers opførsel i ikke-ideale systemer. Den samlede koncentration i en fase eller i en miljømæssig del beregnes som produkt af den samlede aktivitet og aktivitetsevnen, dvs. evnen en fase eller del har til at absorbere et kemikalie. Aktivitetsmetode er et alternativ til den velkendte fugacitetsmetode.

På den metode blev en multimedie aktivitetsmodel for ioniserbare stoffer (MAMI) opstillet og testet. MAMI omfatter pH og ionstyrke afhængighed, samt species-specifik beregning af fordelingskoefficienter. Modelvalidering foretaget med udvalgte ioniserbare kemikalier på et regionalt scenario påviste indflydelsen af dissociering, elektriske vekselvirkninger med partikler, luftfugtighed og i mindre grad havvands saltholdighed, på forudsagte miljømæssige koncentrationer af ioniserbare stoffer. Egenskaberne af MAMI er i sammenligning med en konventionel fugacitetsbaseret model beviset på, at aktivitet metoden kan udvide anvendelsesdomænet og forbedre eksponeringsmodellernes forudsigelser. Endeligt er pH og pK_a værdier som beskriver ionisering blandt de mest vigtige modelparametre og skulle omfattes i probabilistiske eksponeringsvurderinger.

1. Introduction

1.1 Chemicals risk assessment

Our daily life benefits from the use of chemicals. Products that have not benefited from the use of manufactured chemicals can hardly be found in our supermarkets. Manufactured chemicals protect crops (pesticides), husbandry (veterinary pharmaceuticals), our health and appearance (pharmaceuticals and personal care products) and are used to process, to preserve and to color and to improve the quality of materials, packages, textiles, food and beverages and many other products (industrial chemicals). Industrial applications of organic and inorganic chemistry have introduced to the market an increasing number of chemicals. Chemicals improve the quality of our lives but may be harmful to humans and to the environment.

Almost all substances are toxic over a certain dose, as Paracelus stated in the XV century: "*Dosis sola facit venenum*". Toxicity depends on the dose and on the target organism. Some chemicals are toxic to organisms even at very low concentration, some have endocrine disrupting properties, and others are carcinogenic. Some are persistent in the environment, which means that they are not degraded. Depending on their physicochemical properties, chemicals can be transported over long distances. Some tend to accumulate in living organisms and their concentration increases along food chains in ecosystems (Trapp and Matthies 1998).

Humans may be directly exposed to chemicals from consumer products or at workplace. Chemicals may be emitted into the environment during production, transport or use as well as after waste disposal. In the environment, they can be transported, even to remote areas, via air, water, soil, sediments and even via living organisms; they can be degraded by biotic and abiotic processes. Chemicals may accumulate in biota and have adverse effects on ecosystems, even in remote areas (United Nations 2001). Indirect human poisoning may occur via inhalation, drinking water, ingestion of food products or other exposure pathways (European Chemicals Agency (ECHA) 2009a).

The awareness of members of the public, scientists, policy- and decision makers and of the industry itself about the potential adverse effects of chemicals on humans and on the ecosystem has increased over the last years. Consequently, chemicals are being increasingly controlled and regulated. An appropriate regulatory response to the risk associated with chemicals released into the environment (chemicals risk management) requires a science-based characterization of the risk (chemicals risk assessment). Risk assessment is fit for regulatory purpose because it provides a synthetic output to a complex question by using a scientifically accepted approach (Van Leeuwen and Vermeire 2007). It is an interdisciplinary discipline that involves chemists, (eco)toxicologists and environmental scientists. It combines the (eco)toxicological information of a substance (hazard assessment) with the prediction of exposure to

humans and the environment (exposure assessment) to characterize the risk (risk characterization). Hazard assessment, or effect assessment, refers to the evaluation of the inherent capacity of a chemical to cause adverse effects on a living organism. Exposure assessment is the process of estimating the exposure of a population to a chemical. Hazardous chemicals become a risk to humans and the environment upon exposure. Risk characterization is the estimate of the adverse effects likely to occur to humans or to an ecosystem due to the predicted exposure to a chemical. This estimate is typically measured by the ratio (risk characterization ratio) of the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) (Van Leeuwen and Vermeire 2007). The PEC is the predicted concentration in a given environmental compartment, calculated from the exposure assessment. The PNEC is the concentration below which exposure to a substance is not expected to cause adverse effects, calculated from the effect assessment. Values of the risk characterization ratio greater than one indicate a potential risk.

Risk assessment is far from being an exact science and does not aim at it for two major reasons. First, the impossibility for any model to precisely reproduce the real scenario and to provide exact estimations: the complexity of exposure pathways, the variability of environmental conditions, the heterogeneity of populations exposed as well as the uncertainty associated with laboratory tests does not allow certain nor universally valid outputs. Secondly, a simple and reproducible output is preferred to a complex one for the purpose of risk management. Risk assessment should thus be regarded as an evaluative tool based on selected realistic standard scenarios. As such, the concept of chemical risk assessment has been widely implemented in the EU legislation for the evaluation of crop protection products, fertilizers, biocides, veterinary and human pharmaceuticals, cosmetics, food additives and industrial chemicals.

1.2 The REACH regulation

Little is known about the (eco)toxicological effects the 104 000 substances that are marketed in the European Union (European Parliament and Council (EC) 2006). Only a tiny minority of these substances has been risk assessed as a result of the inefficient former legislative framework, which did not produce sufficient knowledge about chemicals' risks. Aiming at improving the protection of human health and the environment through an early identification of potential impacts, the EU adopted a new regulation for the Registration, Evaluation, Authorization and restriction of Chemicals (EC 2006) on June 1, 2007. REACH aims also at maintaining the competitiveness and at enhancing the innovative capability of the EU chemical industry. The regulation replaced a patchwork of many pieces of legislation and streamlines the processes of chemical risk assessment and management. REACH places greater responsibility on industry to assess as well as to manage the risks of chemicals, under the supervision of the European Chemicals Agency (ECHA). Based on risk assessment, the industry must

ensure that chemicals are produced, transported, used and disposed of safely throughout the supply chain. Information requirements depend on the quantity manufactured or imported, starting from the lowest threshold of 1 ton per year. The agency provides technical guidance documents, evaluates registrations and issues authorizations, bans or restrictions. At its entry into force, it was estimated that about 30 000 substances had to be registered by 2018 (ECHA 2008). These numbers size the challenge that all stakeholders involved in the implementation of REACH are facing.

The optimization of testing strategies and the refinement of risk assessment models is not only an economic need to reduce the costs of REACH. The rigid application of testing schemes, as required by the former legislation, to generate (eco)toxicological data would drastically increase animal testing. The REACH regulation explicitly seeks to balance the level of protection of human health and the environment against animal welfare. The goals of REACH are very ambitious. However, a comprehensive technical description on how to evaluate this huge number of chemicals is yet missing. To improve testing and non-testing strategies for their use in risk assessment, the EU Commission funded the integrated research project OSIRIS "Optimized Strategies for Risk Assessment of Chemicals based on Intelligent Testing" (www.osiris-reach.eu). The overall objective of OSIRIS is to develop integrated testing strategies fit for regulatory purposes that fulfil both safety levels and animal welfare goals, and that are practicable from both a technical and an economic perspective. Particular attention is paid throughout the project to examine the applicability domain, the limitations and the uncertainty inherent to each method applied. Within OSIRIS, the Department of Environmental Engineering of the Technical University of Denmark (Stefan Trapp) is coordinator of Work Package 3.1 "Environmental Exposure", whose major objective is the refinement of environmental exposure and bioaccumulation models used for risk assessment of chemicals.

1.3 Problem definition and objectives

In chemical risk assessment, environmental exposure is estimated with mathematical models, which consider transport and bioaccumulation of substances released into the environment. Environmental exposure covers the exposure of organisms and humans via air, water, soil and food. Current exposure models, such as Simplebox (Brandes et al. 1996), the multimedia fate model included in EUSES (European Union System for evaluation of Substances), were originally developed for neutral chemicals. These models, as described in the Technical Guidance Documents (TGD) in support of REACH (ECHA 2009a), are based on algorithms that are not necessarily valid for dissociating and polar compounds. However, many of the chemicals currently under regulatory scrutiny are polar or ionic. Ions behave differently from neutral molecules, their fate being influenced by electrical interactions. Chemical speciation, electrical interactions with other charged species, adsorption to non-biotic

and biotic surfaces, and transport across biological membranes are some of the crucial fate processes involved. These processes, as well as their pH dependency, are usually not considered by existing models described in the TGD. It is therefore an urgent need, particularly, but not only, in the REACH context, to review and to adapt existing methods or, if necessary, to develop new ones that are suitable for the estimation of environmental exposure of ionizable chemicals.
The main objectives of the present PhD research project are:

- To investigate the physicochemical properties of REACH chemicals and assess the occurrence of ionizable chemicals.
- To identify limitations of existing methods and, if needed, develop new equations for the estimation of environmental partitioning (sorption and bioaccumulation) and its pH dependency for ionizable chemicals.
- To identify limitations of existing exposure models to ionics and to present a new convenient mathematical framework based on the chemical activity (activity approach).
- To develop a multimedia environmental exposure model suitable to ionizable chemicals and test it against environmental data and other existing models to identify improvements.
- To perform the model sensitivity analysis and to identify the major sources of uncertainty by giving examples of probabilistic exposure assessment.

Chapter 1 introduces the basic concepts of chemicals risk assessment, as adopted by the EU legislative framework. Chapter 2 introduces the physicochemical properties determining the environmental behaviour of organic pollutants and the specific characteristics of ionizable chemicals in the context of exposure assessment. Chapter 3 illustrates the improvements in the prediction of environmental partitioning of organic ionics. Chapter 4 introduces the principles of environmental multimedia modeling and presents a novel mathematical framework suitable for multispecies ionics (the activity approach). Chapter 5 presents the implementation and test of a Multimedia Activity Model for Ionics (MAMI), based on the activity approach. This chapter includes a validation study with 2,4-D, aniline and trimethoprim and the uncertainty analysis of the model.

2. Organic ionizable chemicals

2.1 Organic ionics in the chemical industry

Ionizable organic chemicals, herein forth also referred to as "ionics", are organic substances with one or more dissociating group in their structure. In an aqueous solution they are partially present as electrically charged molecules according to their dissociation constant. Ionizable chemicals can be acids, bases, amphoters and zwitterions or salts and comprise a large fraction of pesticides, human and veterinary pharmaceuticals as well as industrial chemicals.

The occurrence of organic ionics is higher for classes of chemicals with a specific biological target. The ionization state influences the efficiency of a compound to hit a specific biological target. Thus, the percentage of ionizable substances is particularly high among pharmaceuticals. About 77% of the substances within the World Health Organization list of essential medicinal drugs have an ionizable group (Manallack 2007). Many drugs targeting the central nervous system, including illicit ones, and in particular those derived from alkaloids, are weak bases or ampholytes (Manallack 2007).

About one third of modern pesticides are ionic, mostly anionic (from the pesticide database: Footprint 2009). The ionization state of a pesticide determines not only the capability to hit a specific biological target, but also the mobility of the compound in soil and thus its potential to be taken up by plants (Trapp 2004). Some classes of plant protection products are typically ionizable compounds. Many systemic herbicides are weak acids; systemic fungicides are typically weak bases (Footprint 2009). Pesticides are one of the most important and studied class of contaminants. Concerns about the toxicity to non-target organisms, the potential for bioaccumulation and for widespread contamination have urged the development of new products. Over the last decades, there has been an increasing trend in agricultural practice to replace lipophilic and biologically non-target specific compounds with polar (non-volatile) and target-specific active substances. This trend not only responds to environmental concerns but has also enhanced the efficiency of plant protection products.

In the early years of environmental chemistry, the focus was on organo-chlorine pollutants. Concerns were raised due to their persistence, bioaccumulation, global transport and toxic potential. A second factor was that chlorinated compounds were also easy to measure in small amounts due to the invention of the electron capture detector by J.E. Lovelock in 1957. In recent years, novel analytical methods have become available for the detection of polar and ionic compounds in environmental matrices, examples being the high performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS). Subsequently, it was increasingly recognized that organic ionics (e.g. pharmaceuticals, pesticides) are ubiquitously present

in surface waters (Ternes 1998, Zuccato et al. 2004 Kolpin et al. 2002), sediments (Pouliquen et al. 2009), soils and groundwater (Sacher et al. 2001, Baun et al. 2004, Thiele-Bruhn 2003) and even in the atmosphere (Yao et al. 2008)

2.2 The REACH chemical space

As a whole, the chemical industry involves extremely diverse chemical classes. The majority are organic chemicals, but the chemical space is more complex and includes metals, organometallic substances, salts of organic ionics, inorganic salts and nanomaterials. Ionizable organic groups such as carboxylic acids, phenols, amines and anilines, are frequent in many organic industrial chemicals. A particular class of ionizable organics are ionic surfactants, very frequent in detergents, dyes, pigments, adhesives and other products. The occurrence of ionizable organics among industrial chemicals is poorly known. A screening study was then performed on a representative sample of substances pre-registered for the EU regulation REACH.

About 143 000 industrial chemicals have been pre-registered at the European Chemical Agency to comply with the EU Regulation for the Registration, Evaluation, Authorization and restriction of CHemicals (EC 2006, ECHA 2009b). About 117 000 are due to registration by 2010 (production >1000 t/y, >100 t/y and very toxic, >1 t/y and carcinogenic, mutagenic or toxic to reproduction) or 2013 (>100 t/y). A random sample of these chemicals was selected and processed using the software ACD/Labs® (ACD/I-Lab, ver 6.01, Advanced Chemistry Development, Toronto ON, Canada) for the calculation of the negative decadic logarithm of the dissociation constant(s) (pK_a), the octanol-water partition coefficient of the neutral molecule (log P, also known as log K_{OW}) and the vapour pressure of the neutral molecule (p_s) (Franco et al. 2010, Appendix 1). The analyzed sample covered approximately 1.5% of all the 143 000 pre-registered REACH chemicals.

About one half (49%) of the compounds are partly or totally ionized under environmental conditions (pH 4 to 10) (Figure 1). The majority of ionizable chemicals are acids (27%) but also bases (14%), amphoters and zwitterionics (8%, molecules including both acidic and basic groups) are frequent. About 18% of the total sample comprises multivalent ionics, most of them acids. One third of the total sample (33%, i.e. most of the ionizable) comprises chemicals that are mostly ionized at pH 7 ($pK_{a,acid} < 7$ or $pK_{a,base} > 7$).

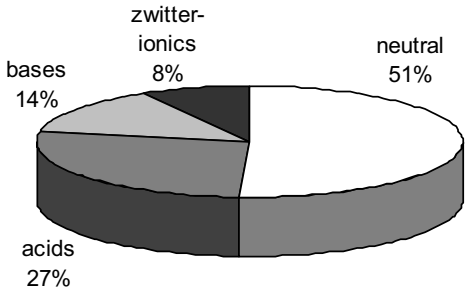

Figure 1. Percentage of ionics from 1510 pre-registered REACH chemicals. Only acid pK_a < 12 and basic pK_a > 2 are considered. Zwitterionics include amphoters.

The octanol-water partition coefficient of the neutral molecule (log *P*), describing the lipophilicity of the analysed chemicals, varies over more than ten orders of magnitude (Figure 2). The most frequent log *P* values range between 0 and 4. There is a high occurrence of hydrophilic chemicals (30% with log *P* < 1). Super-lipophilic chemicals are also frequent (10% with log *P* > 6). The apparent octanol-water partition coefficient at pH 7 (log *D*), is lower than log *P* if the chemical ionizes. The substances mostly ionized at pH 7 (in grey in Figure 2) are frequently polar in the neutral form, but lipophilic ionics occur as well. In particular, 28% of the substances with a log *P* > 6, 3% of the total sample analyzed are mostly ionized at pH 7. Long lipophilic structures with a ionizable head (e.g. surfactants) fall into this category.

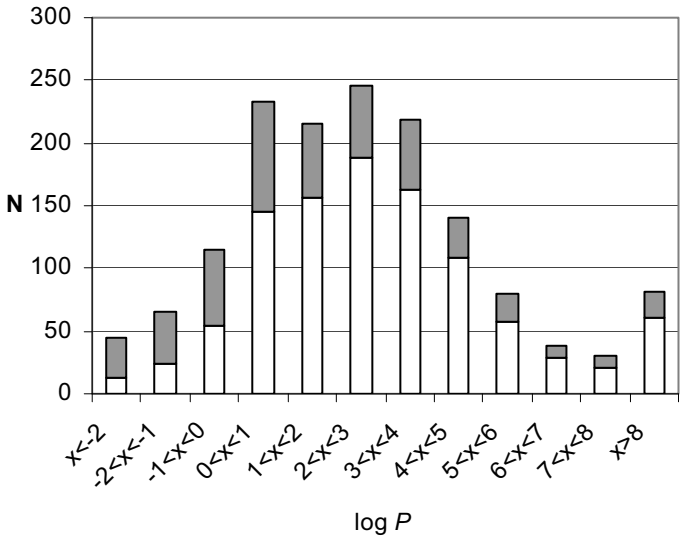

Figure 2. Distribution of the octanol-water partition coefficient of the neutral molecule (log *P*) of the 1510 analysed pre-registered REACH chemicals. The fraction of chemicals that are mostly ionized at pH 7 (p$K_{a,acid}$ < 7 or p$K_{a,base}$ > 7) is marked in grey.

The high occurrence of ionizable chemicals poses two major challenges to risk assessors: the increased testing requirements for regulatory purposes and the limited applicability domain of currently used models. Estimation methods may not be applicable to ionizable chemicals. In this case, tests are required and these should preferably cover both sides of the environmentally relevant pH-range (ECHA 2009a). It is therefore important to extend the applicability domain of existing models and refine model predictions, taking into account the effect of pH. In the context of environmental exposure assessment, this applies to key properties such as the soil-water partition coefficient and the bioaccumulation factor, as well as to exposure models for the prediction of environmental concentrations.

3. Speciation and environmental partitioning

3.1 Speciation equilibria

Ionizable compounds dissolved in water increase the electric conductivity of the solution and were named "electrolytes" by M. Faraday. Weak electrolytes are only partly dissociated in aqueous solution under normal pH conditions, while strong electrolytes dissociate (almost) completely. According to their electrical charge ionizable chemicals include monovalent, bivalent or multivalent acids or bases, amphoters and zwitterions (i.e. structures with both acids and basic groups) and salts. In water, acids release H^+, in the form H_3O^+, according to the reaction:

$$AH + H_2O \leftrightarrow H_3O^+ + A^-$$

Bases attract H^+ forming negative hydroxyl ions OH^- in solution:

$$B + H_2O \leftrightarrow BH^+ + OH^-$$

Speciation equilibria are described by the active concentration of the species participating in the reaction. Under ideal conditions, the active concentration or chemical activity (a) is equal to the free dissolved concentration (Lewis 1907). The equilibrium constants of acid/base reactions (the acid dissociation constant K_a and basic dissociation constant K_b) are the ratio of the activity products of reagents and products,

$$K_a = \frac{[H_3O^+]\,[A^-]}{[AH]} \tag{1}$$

$$K_b = \frac{[BH^+]\,[OH^-]}{[B]} \tag{2}$$

where the activity of water $[H_2O] = 1$ and drops out. The dissociation constant is usually given as negative $\log_{10}$:

$$pK_a = -\log_{10} K_a \tag{3}$$

The pK_b value of a base can be calculated from the pK_a of its conjugated acid and the ion product of water, $K_W = 14$ (Henderson 1908).

$$pK_b = 14 - pK_a \tag{4}$$

For a monovalent compound dissolved in pure water, the activity fractions of neutral molecules (ϕ_n) and ions (ϕ_i) are determined by the *Henderson-Hasselbalch equation*:

$$\phi_n = \frac{1}{1+10^{\alpha\,(pH-pK_a)}}$$
$$\phi_i = 1-\phi_n \qquad (5)$$

where α is 1 for acids and -1 for bases. Bivalent acids and bases undergo a two-step dissociation reaction to form bivalent ions.

$AH_2 + 2\,H_2O \leftrightarrow A^- + H_3O^+ + H_2O \leftrightarrow A^{--} + 2\,H_3O^+$ (bivalent acids)

$B + 2\,H_2O \leftrightarrow BH^+ + OH^- + H_2O \leftrightarrow BH_2^{++} + 2\,OH^-$ (bivalent bases)

In this case, the fractions are determined by the first and the second dissociation constants , pK_{a1} and pK_{a2}:

$$\phi_n = \frac{1}{1+10^{\alpha\,(pH-pK_{a1})}+10^{\alpha\,(pH-pK_{a1})+\alpha\,(pH-pK_{a2})}}$$
$$\phi_i = \phi_n \cdot 10^{\alpha\,(pH-pK_{a1})}$$
$$\phi_{2i} = \phi_n \cdot 10^{\alpha\,(pH-pK_{a1})+\alpha\,(pH-pK_{a2})} \qquad (6)$$

where α is +1 for acids and -1 for bases. Amphoters are molecules that can form acid or basic species from their neutral form. For amphoters, always p$K_{a,acid}$ > p$K_{a,base}$.

$H_2R^+ + OH^- \leftrightarrow HR + H_2O \leftrightarrow R^- + H_3O^+$

Usually, the acid and the basic moieties are distinct in the structure of an amphoter. Sometimes, it can be the same moiety that acts as acid at high pH and as base at low pH (e.g. ammonia, water). The equations for the speciation of an amphoter are:

$$\phi_n = \frac{1}{1+10^{pH-pk_{a,acid}}+10^{pk_{a,base}-pH}}$$
$$\phi_- = \phi_n \cdot 10^{pH-pk_{a,acid}}$$
$$\phi_+ = \phi_n \cdot 10^{pk_{a,base}-pH} \qquad (7)$$

where ϕ_- and ϕ_+ are the anionic and cationic fractions. Zwitterions are molecules that carry a net neutral electrical charge while having formal positive and negative charges on different atoms. For zwitterions $pK_{a,base} > pK_{a,acid}$.

$$RH_2^+ + OH^- \leftrightarrow HR^{+-} + H_2O \leftrightarrow R^- + H_3O^+$$

The equations for the speciation of a zwitterion are:

$$\begin{aligned} \phi_n &= \frac{1}{1+10^{pH-pk_{a,base}}+10^{pk_{a,acid}-pH}} \\ \phi_- &= \phi_n \cdot 10^{pH-pk_{a,base}} \\ \phi_+ &= \phi_n \cdot 10^{pk_{a,acid}-pH} \end{aligned} \quad (8)$$

In general, the fraction of neutral species calculated by Eqns. 7 and 8 is the sum of the two globally neutral species (R and R^{+-}). For amphoters, the zwitterionic fraction can be neglected when $pK_{a,acid} >> pK_{a,base}$. For zwitterions, the uncharged species can be neglected when $pK_{a,base} >> pK_{a,acid}$. If the acid and basic dissociation constants are close, the unionized and the zwitterionic species coexist. In this case, ϕ_n is the sum of the two globally neutral species and must be calculated using the macroscopic dissociation constants (referring to the stoichometric ionization). The ratio of zwitterionic and unionized species, known as constant of tautomeric equilibrium, K_Z, determines the fraction of the two neutral species (Bouchard et al. 2002).

3.2 Physicochemical properties

The affinity of organic chemicals to different media (air, water, soil and sediments) is determined by their physicochemical properties. The volatility, expressed by the vapour pressure (p_s in Pa) determines the affinity to air; the solubility (*sol*, in mol/L) determines the affinity to water; the octanol-water partition coefficient (K_{OW}) describes the relative affinity to lipophilic phases such as lipids or the organic matter in soil and sediments. Vapour pressure, solubility and octanol-water partition coefficient have traditionally been used for predicting the environmental fate of neutral lipophilic organic chemicals (Mackay 2001).

Ionizable organics are present in the environment as neutral and charged species according to the pK_a and the pH (Eqns. 5-8). The physicochemical properties of ionic species differ from the properties of their correspondent neutral species. The vapour pressure of ions is negligible ($p_{s,i} = 0$) while the solubility is very high. The octanol-water partition coefficient is on average 3.5 log units lower than the K_{OW} of the correspondent neutral species (Trapp and Horobin 2005).

In addition to these properties, the environmental behaviour of ions is also influenced by the electrical charge. Anions and cations are repulsed from surfaces or electrical fields of the same charge, while they are attracted by opposite charges, to which they may bind electrically.

3.3 Environmental partitioning: neutral vs. ionic molecules

The principle that governs the equilibrium distribution of organic chemicals in different environmental phases is the minimization of the Gibbs free energy, G (J), which corresponds to the maximization of the entropy in the system. At thermodynamic equilibrium (minimum G), the chemical potential of a substance is equal in all phases (Mackay 2001).

The distribution of organic chemicals across environmental phases can be described by an evaluative model consisting of air, water soil and sediments and biota. Three key partition coefficients describe the equilibrium distribution in these compartments: the air-water partition coefficient K_{AW}, the solid-water partition coefficient K_d and the bioaccumulation factor BCF.

The non-dimensional Henry's law constant (K_{AW}) is the ratio of activities in pure water and gas. The K_{AW} is often confused with the concentration ratio, which is correct only under ideal conditions. For neutral molecules, it can be estimated from the ratio of vapour pressure and solubility. The K_{AW} of ions is zero because $p_{s,i} = 0$. The air-water partition coefficient is then related to the fraction of neutral molecules in water ($K_{AW,n}$).

For the solid-water partition coefficient and the BCF of neutral molecules, a similar paradigm, based on the molecules' lipohilicity, has been applied. Organic chemicals tend to sorb primarily to the lipophilic organic matter (OM) present in soil and sediments (Schwarzenbach et al. 2001). Analogously, organic chemicals mainly accumulate in the lipid fraction of biota. Hydrophobic interactions are driven by Van der Waals forces, second-order bonds often found between apolar molecules (Schwarzenbach et al. 2001). Traditionally the octanol-water partition coefficient has been used as a surrogate for lipophilic organic matter. The organic matter itself is usually expressed as fraction of organic carbon (OC). Linear regression equations based on the K_{OW} are used to estimate the sorption to solids and the accumulation in biota:

$$\log K_{OC} = a \ \log K_{OW} + b \tag{9}$$

$$\log BCF = c \ \log K_{OW} + d \tag{10}$$

Equations of this type do not consider directly the contribution of polar interactions to partitioning, though their accuracy is acceptable for neutral substances (ECHA 2009a, Brown and Wania 2009).

There are two major challenges for the estimation of sorption and bioaccumulation of ionizable chemicals. First, partitioning is determined by the contribution of all species present (Figure 3). The generic equation for the overall partition coefficient (K_t) of a multispecies chemical is:

$$K_t = \phi_n K_n + \sum \phi_{ion} K_{ion} \quad (11)$$

where ϕ_n and ϕ_i are the fractions of neutral and ionic species and K_n and K_i the species-specific partition coefficients. The overall partition coefficient is then described by the physicochemical properties of the single species.

Secondly, the mobility of ions is influenced by electrical charges. Charges are present in the environment as part of the solid molecular structure of organic and mineral colloids of soils, sediments and other solid particles, and as free ions, mostly inorganic, dissolved in aqueous solution (e.g. seawater).

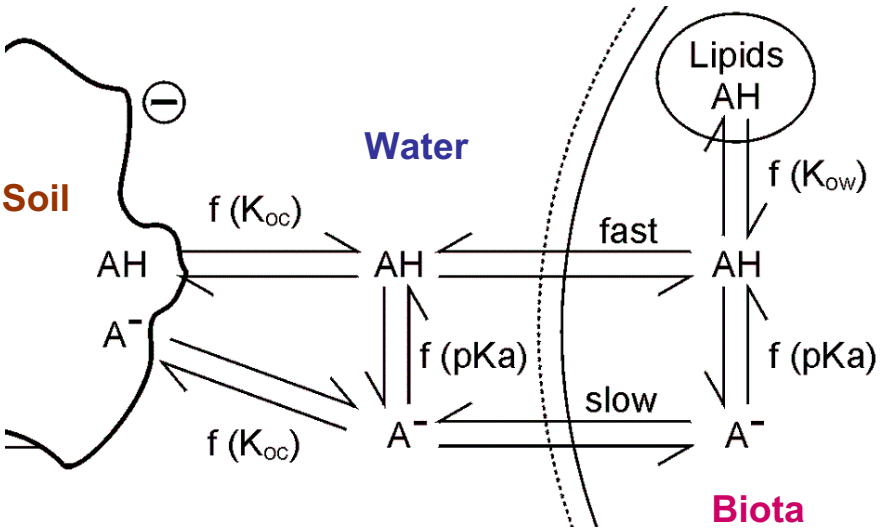

Figure 3. Conceptual model describing the distribution of ionizable organic chemicals between solid, water and biota (source: Trapp 2000)

In presence of an electrical field, the ratio of chemical activities (a) of an ionic species with valency z between two phases, a_1/a_2, theoretically depends on the electrical potential (E in V) and on the Faraday constant (F, in C/mol) according to the *Nernst equation*:

$$\frac{a_1}{a_2} = e^{\frac{-zEF}{RT}} \quad (12)$$

where R is the universal gas constant (m^3 Pa mol^{-1} K^{-1}) and T the absolute temperature in Kelvin. For biota, Eqn. 12 applies to biomembranes characterized by an electrical potential between the inner and the outer phase (Trapp and Horobin 2005).

Besides the lipophilic organic matter, other components in solids, water and biota play a significant role in the partitioning behaviour of non-lipophilic compounds such as ionizable organics. Polar and ionic interactions are typically ignored by traditional methods for estimating partition coefficients such as single parameters linear free energy relationships (SP-LFERs). Polyparametric linear free energy relationships (PP-LFERs), based on the solute and phase descriptors introduced by Abraham (1993), have improved the predictive power and enlarged the applicability domain of estimation methods to polar molecules (Breivik and Wania 2003, Schüürmann et al 2006). However, the Abraham descriptors do not specifically cover ionization. It is widely known that ionization has a strong impact on the partitioning of organic ionics (Schwarzenbach et al. 2001), and yet simple species-specific models in the form of Eqn. 11 have been only applied to interpret observed pH-dependent distributions of partition constants, but not to improve estimation methods.

3.4 Solid-water partitioning

The tendency of a substance to sorb to soil, sediment or particles is typically described by the equilibrium concentration ratio between solids and water, K_d. Since the K_d is highly correlated to the fraction of organic mater in soils or sediments, it is convenient to normalize it to the OC (Mackay 2001):

$$K_{OC} = \frac{K_d}{f_{OC}} \tag{13}$$

In literature, the same notation (K_{OC}) is used for the real organic carbon-water partition coefficient and for the soil-water partition coefficient normalized to organic carbon. The two quantities are identical, if organic carbon is the only component of a solid phase that contributes to sorption. The K_{OC} defined by Eqn. 13 is the soil-water partition coefficient normalized to organic carbon. When components other than OC contribute to sorption, the K_{OC} calculated by Eqn. 13 is higher than the true organic carbon-water partition coefficient. It was postulated that the K_{OC} is not a valid quantity for the calculation of the K_d of ionizable substances because ionic interactions do not only occur in the OC, but also in other soil components such as clay minerals (Schwarzenbach et al. 2001). However, the OC correlates on average better than the clay content to the sorption coefficient, also for ionizable chemicals (Delle Site 2001). Yet, no rigorously tested method was available to predict the K_d or K_{OC} for the majority of organic ionics.

For the present study, experimental log K_{OC} values were collected from literature. The dataset included 93 monovalent acids, 65 monovalent bases and six amphoters (Franco and Trapp 2008, Appendix 2). The few data collected for multivalent compounds were insufficient for a comprehensive and statistically significant analysis and were thus excluded. A correlation study between pK_a and log K_{OW} with the experimental log K_{OC} data showed no clear trend between the dissociation constant and the log K_{OC} for both acids and bases (Appendix 2, Figure 2). Significant correlation was found between log K_{OW} and log K_{OC} for weak acids (pK_a > 7.5), weak bases (pK_a < 3) and strong bases (pK_a > 7.5), but not for strong acids (pK_a < 4) (Appendix 2, Figure 3). It was observed that strong sorption of cations occurred even at relatively low values of log K_{OW}, which makes it unlikely that the process behind is lipophilic sorption.

Species-specific regressions for the estimation of the soil-water partition coefficient normalized to OC were derived for monovalent acids, bases and amphoters. A species specific sorption model (from Eqn. 11) was applied to the K_{OC}:

$$K_{OC} = \phi_{\mathrm{n}} \cdot K_{OC,\mathrm{n}} + \phi_i \cdot K_{OC,i} \tag{14}$$

Applying Eqn. 9 both for the neutral and the ionic fractions gives:

$$\log K_{OC} = \log\left(\phi_{\mathrm{n}} \cdot 10^{a \cdot \log K_{OW,n} + b} + \phi_i \cdot 10^{c \cdot \log K_{OW,i} + d}\right) \tag{15}$$

The first term quantifies the lipophilic absorption of the neutral fraction; the second quantifies the contribution of the ionic fraction (which is probably the sum of lipophilic absorption and electrical adsorption). The dataset was divided into a training set of 62 acids and 43 bases, used for fitting, and an independent set of 31 acids and 22 bases, used for the validation.

The log-linear regressions in the form of Eqn. 9 could be fitted by the least squares method using the data analysis package in Excel®. Regressions in the form of Eqn. 15 were fitted using the non-linear least squares function in the software R for statistical computing (ver 2.5.1). The preciseness (the distance between predicted and experimental values) was evaluated by the mean absolute error (MAE).

$$MAE = \frac{\sum_{i=1}^{n} \sqrt{(y_i - x_i)^2}}{n} \tag{16}$$

Two separate approaches were used to fit Equation 15 to the collected log K_{OC}-values. In the first one, the exponentials in the first and the second term of Equation 15 were fit separately with a linear regression in the form of Equation 9, using the dataset of weak and strong acids (Appendix 2: Eqns. 13 and 14 in Table 2) and bases

(Appendix 2: Eqns. 17 and 18 in Table 2). No dissociation for weak acids and bases and complete dissociation for strong acids and bases were assumed. In the other approach, the full training set was fit directly to determine all parameters at once (Appendix 2: Eqns. 16 and 20 in Table 2). Results of the fits (Appendix 2: Eqns. 13-21 in Table 2) were reported together with quality parameters for the training and the validation set.

The performance of the regressions obtained was satisfactory, with a mean error of approximately 0.5 log units on K_{OC} for monovalent acids, bases and amphoters. For acids, it was superior to the non species-specific regression suggested in the EU technical guidance document (MAE = 0.74). For bases, no regression is given in the TGD.

The process behind sorption of bases is most likely electrical adsorption and sorption is correlated to the pK_a. Surprisingly, a significant correlation was also found between the log K_{OW} and the log K_{OC} of hydrophilic bases (Appendix 2, Figure 6). It was hypothesised that the transport of hydrophilic molecules from the bulk soil solution into the organic matter is limited by diffusion through the OM itself. The regression for bases was then reformulated introducing a term (*f*) accounting for diffusion-limited transport of cationic hydrophilic molecules:

$$\log K_{OC} = \log\ (\phi_n \cdot 10^{a \cdot \log K_{OW,n} + b} + \phi_i \cdot 10^{pKa^c \cdot f^d}) \qquad (17)$$

where

$$f = \frac{K_{OW}}{K_{OW} + 1} \qquad (18)$$

In Eqn. 18, the K_{OW} is the apparent octanol-water partition coefficient at pH 7. Eqn. 17 proved more accurate for the validation set than the fit of Eqn. 15.

The fair agreement of the proposed equations with experimental data confirms that the K_{OC} approach is useful also for ionic organics. This may be because other constituents of bulk soil, such as clay or other minerals, contribute less to the overall sorption. A second reason may be that the content of clay is often correlated with the content of organic matter (Stevenson 1994) and its contribution may be correctly quantified, although indirectly. The proposed equations may therefore fail, if soil or sediment samples show an unusual ratio of organic carbon to clay (or other sorbing matrices), or if the adsorption to another fraction than organic carbon is exceptionally high. Examples are acridine and benzo[*f*]quinoline, two outliers of the validation set for bases. For these two compounds, sorption was underestimated, probably due to their special affinity to the negatively charged clay (Zachara et al. 1990).

The regressions obtained do not consider the variability of soil pH, which may in some case limit the accuracy of estimates. The simplification was necessary primarily because the pH was not given for many experimental data. Instead, an optimal pH (pH_{OPT}) was defined in the fitting exercise to calculate dissociation. For the data with a specified pH, it was found that the optimal pH for the regressions was on average lower than the measured bulk soil pH, probably due to local acidity near the negative surface of colloids.

The influence of soil pH in the sorption of ionizable chemicals was investigated using a separate dataset of experimental log K_{OC} determined at different soil pH. Distributions covering the relevant pH range were collected for 10 acids and 12 bases (Franco et al. 2009, Appendix 3). For acids, increasing K_{OC} was observed at decreasing pH. For bases the trend was more complex. The pH-dependency can be explicitly expressed from Equation 14:

$$K_{OC} = \frac{K_{OC,n}}{1+10^{\alpha(pH-pKa)}} + \frac{K_{OC,i}}{1+10^{\alpha(pKa-pH)}} \quad (19)$$

The relevant pH for the calculation of dissociation should be the local pH at the sorbing surface, which may differ significantly from the bulk soil pH. This can be accounted by replacing pH_{OPT} with a variable (bulk soil pH) adjusted by a corrective factor (pH + δ):

$$K_{OC} = \frac{K_{OC,n}}{1+10^{\alpha(pH+\delta-pKa)}} + \frac{K_{OC,i}}{1+10^{\alpha[pKa-(pH+\delta)]}} \quad (20)$$

Using the previously derived non pH-specific regressions for the estimation of the species-specific K_{OC}, the parameter δ was fit in Eqn. 20 to predict soil pH-dependent K_{OC} distributions. The approach was successful for acids. An example of the fit curves is shown in Figure 4 for two acids, pentachlorophenol and 2,4-D.

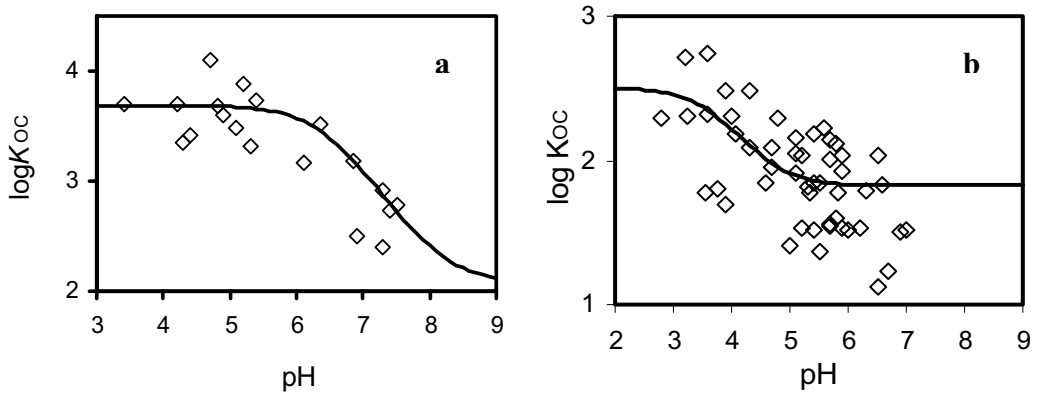

Figure 4. Fit of Equation 20 to the pH-dependent log K_{OC} distributions for pentachlorophenol (a) and 2,4-D acid (b). The only parameter calibrated is the pH-shift δ. The $K_{OC,n}$ and the $K_{OC,i}$ were estimated by the previously fit Eqn. 15, which used an independent dataset for calibration.

The adjusted regression explained well the large variation of K_{OC} with pH (up to two log-units): the mean value of the optimal pH correction shift, δ_{OPT}, was found -0.6.

The modeling theory based on Eqn. 20 can describe the variability of the fractions of neutral and ionic species at different pH. The different speciation at various pH is probably the major reason for the pH-dependency of the soil-water distribution coefficient of ionizable organic chemicals. However, it is not the only one. The pH has in fact a double impact on the total sorption: it influences the speciation of the molecule (sorbate) as well as the soil surface chemistry (sorbent).

The surface of organic colloids in soil is negatively charged due to the ionization of hydroxides and phenolic groups in organic matter and clay. In natural humic acids, the pK_a of these groups ranges from 3 to 5 (Stathi et al, 2007). When the soil pH approaches those values, the surface of colloids becomes less electronegative. Anion repulsion decreases, and the potential for anion exchange with solutes increases; conversely, cations are less attracted and cation exchange becomes less effective (Delle Site 2001).

For acids, both effects (on the sorbate and on the sorbent) favour sorption. Low pH enhances lipophilic sorption of the neutral molecule; at the same time, anions are less repulsed from the sorbent surface, thus anion exchange (and sorption of anions) increases.

For bases, the impact of pH on speciation and on the sorbent surface chemistry has contrasting effects on the total sorption (Figure 5). Cations are electrically attracted by the negative surface of natural colloids in soil. At lower pH, the fraction of cations increases, but simultaneously the protonation of hydroxides and phenolic groups at the sorbing surface reduces the potential for cation exchange. This opposite effects may explain why for some bases optimal sorption occurs when pH ~ pK_a (Delle Site 2001,

Burton et al. 2004). The model used is therefore not able to predict pH-dependent sorption of bases.

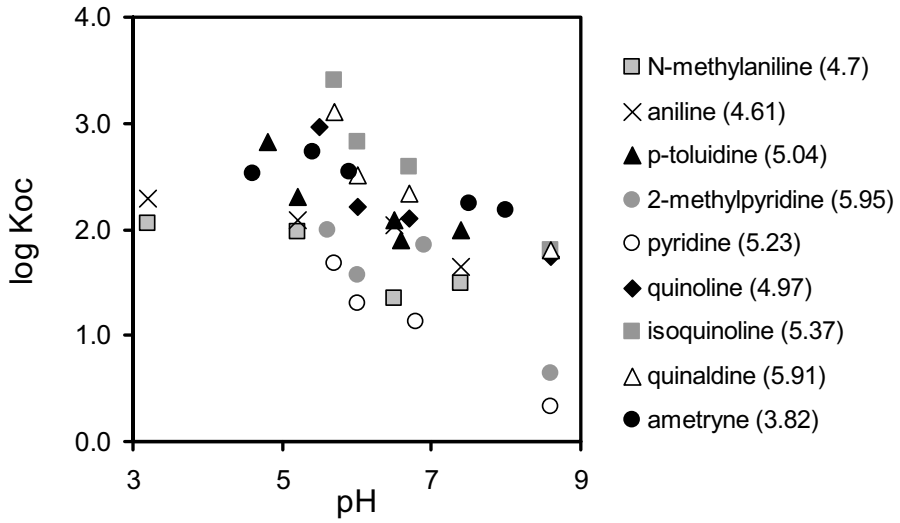

Figure 5. Dependency of the log K_{OC} on the pH for nine weak organic bases (pK_a values given in parenthesis).

Overall, the following equations have been suggested for the prediction of the soil-water partition coefficient normalized to OC of ionizable compounds:

For monovalent acids:

$$K_{OC} = \phi_n \cdot 10^{0.54 \cdot \log K_{OW,n} + 1.11} + \phi_- \cdot 10^{0.11 \cdot \log K_{OW,n} + 1.54} \quad (21)$$

($pH_{opt} = pH_{soil} - 0.6$)

For monovalent bases:

$$K_{OC} = \phi_n \cdot 10^{0.37 \cdot \log K_{OW,n} + 1.70} + \phi_+ \cdot 10^{pK_{a,base}{}^{0.65} \cdot f^{0.14}} \quad (22)$$

($pH_{opt} = 4.5$)

And for amphoters:

$$K_{OC} = \phi_n \cdot 10^{0.50 \cdot \log K_{OW,n} + 1.13} + \phi_- \cdot 10^{0.11 \cdot \log K_{OW,n} + 1.54} + \phi_+ \cdot 10^{pK_{a,base}{}^{0.65} \cdot f^{0.14}} \quad (23)$$

($pH_{opt} = 5$)

It shall be emphasized that the equations above were developed for their use in exposure assessment models. On a more theoretical level, the limits of K_{OW}-based estimations, although species-specific, are well known, in particular for ionic species. A recent experimental study on the sorption of organic acids on pure soil organic matter (Tülp et al. 2009) showed that the ratio of the K_{OC} of the neutral molecule and the anion

is independent of the K_{OW}. The authors claimed that this result stands in contrast with Equation 21. On the other hand, despite investigating a single model soil organic matter, they did not identify any indicator that could consistently explain the observed data. Considering that the definition of K_{OC} in Tülp et al. (2009) is different from the one defined by Eqn. 13, the two studies should not be directly compared. The disagreement is anyway only apparent: the correlation of K_{OW} with the K_{OC} of anions is weak and statistically insignificant (Figure 3 in Appendix 2).

3.5 Bioaccumulation

The potential of chemicals to accumulate from surrounding media into organisms has been recognized as a substantial hazard to wildlife and human health. As a consequence, bioaccumulation is a key criterion in chemical risk assessment (ECHA 2009a). Bioaccumulation describes the ratio of the concentration of a chemical in an organism to the concentration in the surrounding medium. The most common measure of the bioaccumulation potential is the bioconcentration factor (*BCF*) for fish, the ratio of the concentration of chemical in the fish to the concentration in the surrounding water at equilibrium. According to the EU risk assessment framework, a chemical is classified bioaccumulative if $BCF > 2000$ (ECHA 2009a).

It is widely agreed that the *BCF* of neutral organic chemicals is largely determined by lipophilic partitioning into the lipid tissue of fish, which is well described by the octanol-water partition coefficient (Trapp and Matthies 1998). Several regressions between the K_{OW} and the *BCF* exist in the form of Eqn. 10, but none was specifically developed for organic ionics. To estimate the *BCF* of organic acids and bases, a correction of the K_{OW} for the fraction of neutral species is currently suggested in the EU technical guidance documents (ECHA 2009a). This method was never rigorously tested and its validity is questionable, particularly for chemicals that are mostly or completely ionized at environmental pH, because this approach assumes that ions do not biaoccumulate at all. The uptake and distribution of charged molecules in a living cell is not only influenced by the lipophilicity but also by the electrical potential of biomembranes and by the different permeability of the membranes to ions and neutral species. This may lead to an accumulation of ions inside cells (ion trap). These processes can be described by a cell model (Trapp 2004, Trapp and Horobin 2005), which predicts the equilibrium distribution of a substance in a living cell consisting of an aqueous and a liquid phase and surrounded by an electrically charged biomembrane. Diffusion of neutral species is described by the *Fick's first law* of diffusion, while diffusion of ions is described by the *Nernst-Plank equation* (Trapp 2004).

One alternative method is to derive regressions specifically for ionizable compounds. Using experimental *BCF* of monovalent acids and bases collected from the literature, new species-specific regressions were developed for ionics (Fu et al. 2009, Appendix 4). In these regressions, the *BCF* of neutral molecules only depends on the

log K_{OW}, while both the log K_{OW} and the pK_a were used to predict the *BCF* of ions. The equation obtained by fitting the parameters to the training set for acid is:

$$BCF = \phi_n^{(0.64 \log K_{OW} - 0.12)} + \phi_i^{(0.37 \log K_{OW} + 0.06 pK_a - 0.51)} \quad (24)$$

and for bases:

$$BCF = \phi_n^{(0.62 \log K_{OW} - 0.15)} + \phi_i^{(0.28 \log K_{OW} - 0.07 pK_a + 0.84)} \quad (25)$$

These regressions were compared to existing methods for estimating the *BCF* of ionizable organics and to the cell model, using an independent set of data. The best results were obtained with the new regressions (Eqns. 24 and 25) or with the regression developed for neutral compounds and suggested in the EU technical guidance documents (ECHA 2009a), but using the apparent K_{OW} measured at pH 7 as descriptor (log *D*). Both the existing and the new regressions provide reasonable estimates of the *BCF* for monovalent ionizable compounds, with a mean error of approximately 0.4 log units. Ionization typically decreases the *BCF*, but for some compounds, such as moderate acids with pK_a between 3 and 6 and moderate bases with pK_a between 6 and 11, the ion trap effect may decrease or increase the *BCF* depending on the pH gradient. The cell model can predict the effects of the pH-dependent ion trap as well as of the electrical attraction of cations by the negative potential of cytoplasm and of mitochondria. However, it underpredicted the *BCF* of acids, possibly because anions do not accumulate inside the charged cell but rather at the external surface of cells. An advantage of the cell model is that it allows varying the external pH, and it can be adjusted to different types of organisms (e.g. fish cells, plant cells, bacteria)

It was concluded that considering only lipophilic interactions is sufficient to identify bioaccumulative substances, because electrical interactions rarely trigger very high values of *BCF*. To account for the worst case scenario, the *BCF* of acids should be determined at the lower side of the environmental pH range, and the *BCF* of bases at the higher side, when the neutral species are more abundant.

4. Environmental exposure modeling

4.1 Multimedia environmental models

Mathematical models have been developed to understand the behaviour of chemicals in the environment and more specifically to predict their concentrations in air, soil, water, sediments and biota, their overall persistence as well as their potential for long-range transport (Klasmeier et al. 2006). Multimedia environmental models have been successfully developed and implemented in the regulatory framework. These models describe an evaluative environment consisting of homogeneous, well-mixed boxes representing the environmental compartments, typically air, water, sediments, soil and biota. Some compartments are in contact, thus a chemical can migrate between them. The fate of chemicals is described by mass balance equations, which take into account emissions and intermedia transport and loss processes that chemicals may undergo once emitted. Individual phases are assumed in thermodynamic equilibrium within a compartment (e.g. solid, water and gas in soil), but different compartments (e.g. soil and air) are not in equilibrium. Steady-state calculations are preferred, if conditions can be considered constant in time. This is usually accepted to calculate predicted environmental concentrations for the exposure assessment of chemicals. The non-equilibrium steady-state computation corresponds to the level III of complexity described by Mackay (2001). Multimedia models are easily scalable and provide simple and reproducible outputs, which make them suitable for assessing the risk of large number of substances. Time dependent simulations (level IV) may be preferred, if emissions are not constant in time or if steady-state is not reached within reasonable time. Most multimedia models allow running dynamic simulations.

In the EU risk assessment framework, the exposure of the environment to chemicals is calculated by a nested multimedia model, Simplebox (Brandes et al 1996). The model comprises the local, regional, continental and global scale. Environmental concentrations predicted at the regional scale, representing a densely populated and industrialized European region, are considered the background level of contamination. The processes included are emissions, exchange processes across the model boundary (import/export flows in the air and water compartments), loss processes (degradation in all compartments, leaching from soils and burial of sediments) and intermedia exchange processes within the model boundary (diffusion, bulk advective flows, wet and dry deposition from air, runoff and soil erosion, deposition and resuspension of sediments). The computation of mass flows and concentrations in Simplebox is done with concentration-based mass transfer coefficients. The concentration-based approach implemented in Simplebox lacks a common model variable suitable to define equilibrium between compartments. This makes the solution scheme of the mass balance and the calculation and comparison of mass flows computationally unpractical.

4.2 Multimedia fugacity models

The fugacity approach proposed by Mackay in 1979 is a thermodynamically strong and computationally convenient approach for environmental fate modeling of organic chemicals (Mackay 1979). In the last three decades it has become the most popular approach in multimedia modeling.

The term fugacity (*f*) was first introduced in 1901 by G.N. Lewis and indicates the escaping tendency of a chemical from a given phase (Lewis 1901). Fugacity is identical to the partial pressure in ideal gas and has the unit of Pascal. Fugacity can be defined in all environmental phases so that equal fugacities define thermodynamic equilibrium. The basic equation of the fugacity model concept is (Mackay 1979):

$$C = Z\ f \tag{26}$$

where C is the concentration (mol/m^3), f is the fugacity (Pa) and Z is the fugacity capacity (mol m^{-3} Pa^{-1}). The fugacity capacity quantifies the capacity of a phase to absorb a chemical and depends on the chemical and on the nature of the phase or compartment. At equilibrium fugacities are equal and the partitioning ratio between compartments is the ratio of fugacity capacities Z.

Diffusive exchange as well as advective transport and loss processes can be written in the form:

$$\frac{dm}{dt} = D\ f \tag{27}$$

where D-values have the units of mol Pa^{-1} h^{-1} and are defined for each process considered (Mackay 2001). The convenience of the activity approach lies in the possibility to express a complex mass balance in an elegant and compact notation.

Fugacity models are at the same time elegant and widely used. However, they are not applicable to ions, which do not volatilize and do not exert a partial pressure or fugacity. Back in 1979, Mackay observed that chemical activity is preferable to fugacity as model variable for non-volatile chemicals (Mackay 1979).

4.3 The activity approach

The concept of chemical activity was first described by N.G. Bjerrum and first defined by Lewis in 1907 to apply thermodynamic equations to non-ideal systems (Lewis 1907). The chemical activity is related to the chemical potential, μ, which quantifies the energetic state of a substance referred to a reference state, μ^0 (J/mol)

$$\mu = \mu^0 + \mathrm{RT}\ln(a) \tag{28}$$

where R is the universal gas constant (8.314 J mol^{-1} K^{-1}) and T the absolute temperature (K). For solutes, the activity is related to the aqueous concentration (mol/m^3) normalized to a reference state:

$$a = \gamma \frac{C_W}{C_{W,ref}} \quad \text{or} \tag{29}$$

$$a\ C_{W,ref} = \gamma\ C_W \tag{30}$$

where the unitless coefficient γ accounts for the deviation from the ideal solution (i.e. pure water). The standard state, $C_{W,ref}$ can be selected at will, and it is convenient to chose an ideal uni-molar solution (1 mol/m^3) for solutes. Thus, $C_{W,ref} = 1$ for all species and can be incorporated in a for practical purposes, so that (Trapp et al. 2010, Appendix 5):

$$a = \gamma\ C_W \tag{31}$$

where a is the activity in the unit mol/m^3. In an infinitely diluted aqueous solution, activity is identical to the truly dissolved aqueous concentration C_W and to the aqueous equivalent concentration or "aquivalence" formulation introduced to describe the environmental fate of multispecies non-volatile chemicals (Diamond et al. 1992). The concept of chemical activity was established because it is not the total concentration of molecules in solution but an effective or active concentration that drives chemical reactions and environmental processes, such as diffusion and osmotic pressure. According to the Debye-Hückel theory, values of the activity coefficient depend on the valency and on the ionic strength of the solution (Debye and Hückel 1923). For ions, this active concentration is smaller than the total concentration because of ionic interactions ($\gamma_i < 1$); for neutral molecules the active concentration is usually greater than 1 ($\gamma_n > 1$). The total concentration of a multispecies chemical dissolved in water can be express as

$$C_t = a_t\left(\frac{\phi_{n,W}}{\gamma_{n,W}} + \sum_i \frac{\phi_{i,W}}{\gamma_{i,W}}\right) \tag{32}$$

The term in parenthesis links the total activity with the total concentration and is named "activity capacity" (B). The concentration of a multispecies ionizable compound in equilibrium within an environmental compartment consisting of gas, water and solids is

the sum of the concentrations of all species in all phases and can be expressed as a function of the total activity a_t.

$$C_t = a_t \left[G\ \phi_n K_{AW} + W \left(\frac{\phi_{n,W}}{\gamma_{n,W}} + \sum_i \frac{\phi_{i,W}}{\gamma_{i,W}} \right) + S \left(\frac{\phi_{n,S} K_{d,n}}{\gamma_{n,S}} + \sum_i \frac{\phi_{i,S} K_{d,i}}{\gamma_{i,S}} \right) \right] \quad (33)$$

The total activity a_t is the sum of the activities of all species, G, W and S are the volume fractions (m^3/m^3) of gas phase, aqueous phase and solid phase, respectively. The K_{AW} and the K_d are the partition coefficients between air and water and solids and water (m^3/m^3). Only neutral species are present in the gas phase. More generally, the relation between concentration and activity for any environmental compartment can be defined:

$$C = a\ B \quad (34)$$

where B (m^3/m^3) is the "apparent bulk activity capacity" of the compartment. It is "apparent" because related to all species and "bulk" because extended to all phases within the compartment. The activity capacity may be viewed as an analogue to the fugacity capacity Z introduced by Mackay (1979). An advantage of using activity as state variable is that it correctly describes thermodynamic equilibrium of charged and uncharged species in ideal and non-ideal solutions.

Lewis (1907) defined the endpoint of diffusion as equilibrium between compartments (i.e. the state with the highest entropy). For the diffusive flux of neutral molecules between two neighbouring compartments, *Fick's 1st law* applies. For a monovalent ionizable compound the total flux is

$$J = P_n (a_{n,out} - a_{n,in}) + P_i (a_{i,out} - a_{i,in}) \quad (35)$$

where J is the unit net flux of neutral molecules from outside (out) to inside (in) of a compartment (mol m^{-2} h^{-1}), a is the activity of a given species (mol/m^3) and P is the permeability of the boundary (m/h) and is essentially a mass transfer coefficient or velocity. It follows that net diffusion stops (and is then at steady-state) when the activities are equal. Under steady-state conditions, the net flux is zero, and the total activity ratio between inside (in) and outside (out) the compartment is the ratio of in- and outflux J_{in} and J_{out}. Then, the total activity ratio in equilibrium is

$$\frac{a_{t,in}}{a_{t,out}} = \frac{P_n \phi_{n,out} + P_i \phi_{i,out}}{P_n \phi_{n,in} + P_i \phi_{i,in}} = R_{in/out} \quad (36)$$

The endpoint of diffusion defines the equilibrium partition coefficient $K_{in/out}$, the ratio of the total concentrations, which is the ratio of the activity capacities B.

$$\frac{C_{t,in}}{C_{t,out}} = \frac{B_{in}}{B_{out}} = K_{in/out} \tag{37}$$

In a multimedia system, the mass balance can be written in terms of activity and activity capacities. In the same way as the D values were defined in the fugacity approach (in mol Pa^{-1} h^{-1}) (Mackay 1979), T values were defined (m^3/h) in the activity approach to describe intermedia and removal fluxes (in mol/h):

$$\frac{dm}{dt} = a\ T \tag{38}$$

Based on Equations 34 and 38, multimedia activity models can be built parallel in structure to fugacity models. For neutral compounds in dilute systems (low ionic strength), the results from the activity approach are identical to those obtained using fugacity, as long as the same scenario is considered. However, the activity approach goes beyond and can better handle additional processes that occur for ionics, such as dissociation, activity equilibrium, ion trap, electrical attraction and repulsion. Unfortunately, a universal equilibrium criterion cannot be established for ionizable chemicals in all environmental compartments and biota. The activities of individual species may differ significantly across compartments, as the environmental pH ranges from < 2 (aerosol) to > 8 (seawater) (Stumm and Morgan 1981). The sum of the activities of all single species (a_t) is equal between two compartments if the boundary consists of aqueous layers, where all species diffuse at equal rate (e.g. water – sediment). However, neutral and ionic species often diffuse at different velocities. Between air and water, equilibrium is defined by the activity of neutral species because ions do not volatilize. In living cells, due to the lower permeability of biomembranes to ions compared to neutral molecules, diffusive equilibrium is not obtained at equal activities, but at steady state (Trapp 2004).

5. A Multimedia Activity Model for Ionizable chemicals (MAMI)

5.1 Models for multispecies chemicals

Adjustments to the fugacity approach have been proposed to enlarge the applicability domain of multimedia fugacity models to multispecies chemicals including ionics. The "aquivalence" approach formulated by Diamond et al. (1992) was applied on surface aquatic systems to model the fate of mercury and its species (Bhavsar et al. 2004). Toose and Mackay (2004) proposed a simpler multiplier method for modeling chemicals with constant ratios of species concentration. The method was applied on a multimedia model for mercury. Compared to the fugacity approach, the aquivalence equilibrium criterion lacks a strong theoretical basis and it is only valid under ideal conditions. In the field of organic pollutants, Cahill et al. (2003) adapted a fugacity model to predict the fate of speciating chemicals with up to four interconverting species. The model assumes ideal conditions, constant pH and assumes that ionic species are not present in atmosphere. More recently, a multispecies pH-dependent multimedia fugacity model was applied on perfluorooctanoic acid (Armitage et al. 2009). This model features species-specific description of partitioning and exposure pathways (e.g. volatilization only for neutral species). However, it does not present a universally valid concept to handle ionics and, likewise all fugacity models, it is not applicable to pure ions.

5.2 MAMI: model description

The activity approach provides a theoretically strong mathematical framework and combines the compact notation of the fugacity approach with the flexibility necessary to describe pH variability and non-ideal conditions. A Multimedia Activity Model for Ionizable chemicals (MAMI) was developed using the activity approach (Franco and Trapp 2010, Appendix 6). The model consists of air, natural soil, agricultural soil, other soil, freshwater and freshwater sediments, seawater and marine sediments (Figure 6). The dimensions and the properties of the compartments were taken from the EU model for environmental exposure assessment, Simplebox (Brandes et al. 1996) and the EU technical guidance document for chemical safety assessment under REACH (ECHA 2009a).

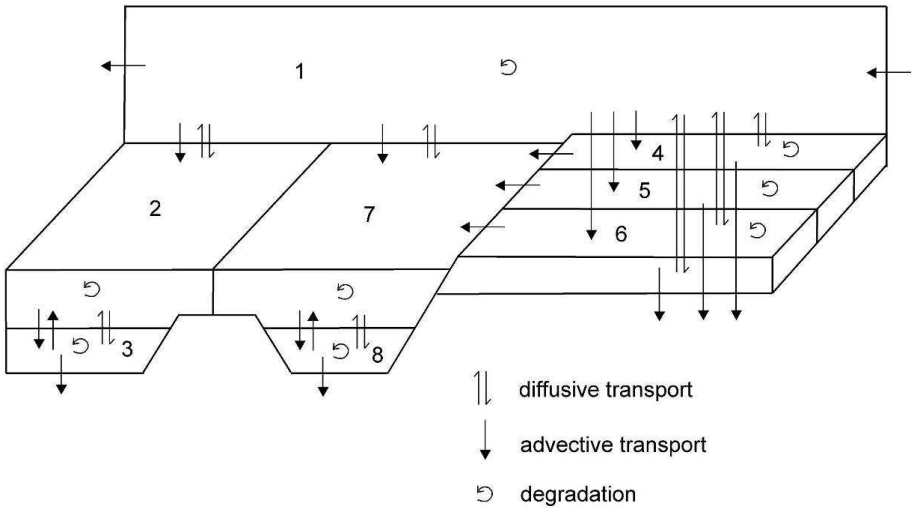

Figure 6. Model compartments and environmental processes in MAMI. The eight compartments are: air (1), natural soil (2), agricultural soil (3), other soil (4), freshwater (5) and freshwater sediment (6), seawater (7) and marine sediment (8).

Compared to Simplebox, the two vegetation compartments were excluded. The two marine compartments can be added or removed facultatively. Additionally, liquid water in air was introduced as aqueous phase associated with the aerosol particles (aerosol moisture) and as cloud water (cloud condensation nuclei). The time and space variability of cloud water in atmosphere is high but, on average, the volumetric fraction of cloud liquid water was found much larger than the fraction of water associated with aerosol. Typical values of pH and ionic strength were chosen within their environmental range. The same intermedia fluxes and removal processes as in Simplebox are included in MAMI (Figure 6). Diffusion to gas phase is limited to the neutral species.

The model is applicable to neutral as well as to monovalent ionizable compounds (acids, bases and amphoters). The physicochemical parameters necessary to run the model are the molar mass (M), the dissociation constant(s) of the acid and/or the basic group ($pK_{a,acid}$ and $pK_{a,base}$), the Henry's Law constant (H_n, in Pa m^3 mol^{-1}) and the octanol-water partition coefficient of the neutral molecule ($K_{OW,n)}$. The model features pH and ionic strength dependency. The fraction of neutral molecules and ions in water are determined by the pK_a using the *Henderson-Hasselbalch* equation. Ionization influences partitioning in air, dry and wet deposition and sorption to soil (Figure 7).

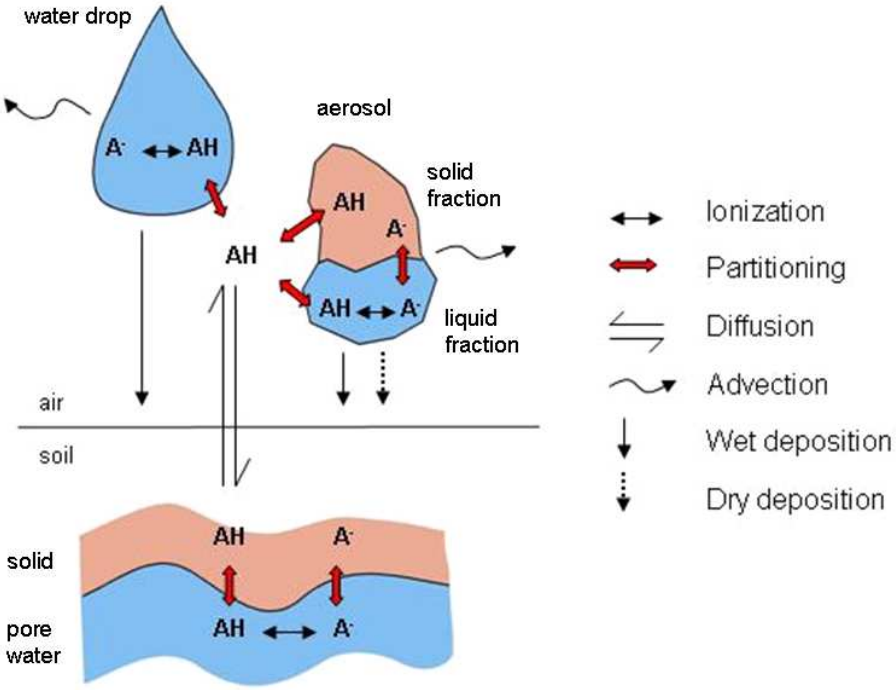

Figure 7. Speciation, species-specific partitioning and transport processes of an organic acid between soil and air as implemented in MAMI.

The model requires species-specific partition coefficients, which are estimated from the physicochemical properties if not available. A dual phase sorption model describes partitioning into wet aerosols and into cloud water. The soil-water partition coefficient normalized to OC, K_{OC}, is calculated from the pK_a and the $K_{OW,n}$ using new pH-dependent regressions developed for monovalent acids, bases and amphoters (Eqns. 21-23). Both the steady-state (level III) and the dynamic version of MAMI (level IV) were developed in Python® and in Excel®. Model outputs can be viewed as species-specific or total apparent PECs and mass distribution.

5.3 A validation study with 2,4-D, aniline and trimethoprim

Multimedia models are evaluative tools used in the context of exposure and risk assessment of chemicals but do not aim at predicting exact environmental concentrations. The environmental variability is hardly represented by homogeneous and well mixed boxes. On the other hand, measured environmental concentrations do not necessarily represent the level of contamination at the regional scale. It is thus difficult to comprehensively validate any multimedia model and yet the model validation is essential to test a new model and to evaluate the performance compared to existing ones.

A validation study of MAMI was carried out for three test chemicals: the herbicide 2,4-D (acid), the aromatic amine aniline and the antibiotic trimethoprim (bases) (Franco and Trapp 2010, Appendix 6). The selected chemicals contain three

different ionizing moieties, namely a carboxylic group (-COOH), an amine ($-NH_2$) and a pyrimidine (-N-), and are all partly ionized in the environment. They represent different emission scenarios and exposure pathways; the first is typical for a pesticide, the second for an industrial intermediate and the third for a veterinary and human antibiotic. A realistic regional exposure scenario was simulated for the three test compounds. Model results were compared to the ones obtained with a conventional fugacity model, also parameterized as the regional scale of Simplebox, and to monitoring data collected from literature. For 2,4-D more than 450 measurements from the Canadian prairie provinces were collected from 29 monitoring stations in air and 24 in freshwaters (rivers, drainage creeks, ponds, wetlands). Yearly average concentrations of aniline were collected from 10 stations along the Rhine river basin (Germany). Environmental concentrations of trimethoprim were collected from monitoring studies from Denmark, England, Wales, France, Germany and the U.S., including more than 350 measurements for freshwaters and 44 for sediments.

The performance of MAMI was satisfactory and in reasonable agreement to the measured data. In some cases, the concentrations predicted with MAMI were closer to the monitoring data than the ones calculated with the conventional fugacity model; in others they were similar. The variability of environmental pH and the different partitioning properties of neutral and ionic species resulted in extremely variable species concentration ratios across MAMI compartments.

Environmental partitioning of ionizable chemicals is best described by a species-specific sorption model that considers both lipophilic and electrical interactions. The effect of salinity is negligible in the terrestrial ecosystem but has an impact in the marine compartments, where neutral species are salted out, whereas ions are salted in.

Model results showed that air humidity, in the form of cloud water, can absorb and transport non-volatile chemicals in atmosphere, which explains the ubiquitous occurrence in the environment of organic electrolytes, such as 2,4-D, on a regional scale. Humidity is therefore a key parameter to correctly describe the fate of polar and ionizable chemicals in air. Environmental observations on the distribution of currently used pesticides on a regional scale (Muir et al. 2004) indicate that the assumptions of dry air and continuous rain may cause a severe overestimation of wet deposition, and an underestimation of the concentration in air and of travel distances for hydrophilic chemicals. The occurrence of dry periods can be taken into account in a multimedia model, as proposed by Jolliet and Hauschild (2005). In the present validation study, it was observed that the inclusion of cloud water in air, as parameterized in MAMI, limits the drawbacks of the assumption of continuous rain. Combining the effects of intermittent rain and variable liquid water content in air with MAMI may provide further insight about the fate of polar and ionizable pollutants in the atmosphere.

5.4 Sensitivity and uncertainty analysis

The definition of model boundaries, the identification of exposure pathways, the mathematical formulation of environmental processes and the selection or estimation of parameters inevitably introduce a degree of uncertainty in all environmental multimedia models. A proper characterization and quantification of model uncertainties can improve the reliability, robustness and accuracy of the exposure assessment and is necessary to statistically justify the introduction of additional parameters and the increased model complexity. The sensitivity analysis (Franco and Trapp 2009a) and probabilistic model simulations (Franco and Trapp 2009b) were performed for a selection of chemicals to identify the major sources of uncertainty in MAMI and, more specifically, to compare the uncertainty of the new parameters added with the typical model uncertainty.

The chemicals selected for this study were benzene 2,4-D, aniline, pentachlorophenol, perfluorooctanoic acid, bisphenol-A, trimethoprim and 4-chloroaniline. Experimental data were collected from literature to fit probability density functions for the chemical dependent properties (physicochemical properties and degradation rates) and for the environmental parameters specifically added to MAMI (pH, ionic strength and liquid water content in air). The probabilistic Monte Carlo simulations on MAMI were performed using the software Crystal Ball® (version 4.0).

The use of species-specific models to predict the environmental exposure of ionizable chemicals is statistically justified because the uncertainty introduced by the additional parameters (e.g. pH and pK_a) is smaller than the typical model uncertainty. The uncertainty of predicted environmental concentrations and of persistence is in most cases explained by the large uncertainty associated with (bio)degradation rates, which may be caused by model assumptions, experimental or estimation errors or by the environmental variability, including the effect of variable pH. The study highlighted the need for updating and refining factors for intermedia extrapolation and default values for the derivation of probability density functions for biodegradation rates. To improve uncertainty analysis in the context of REACH, guidance should be provided to quantify uncertainty associated to degradation rates obtained from screening tests and from simulation tests.

5.5 Opportunities and limitations

The activity approach is analogous, in its mathematical formulation, to the well known fugacity approach. The fugacity approach refers to the gas phase, whereas the activity approach refers to the pure aqueous phase. The applicability domains of the two modeling approaches are complementary: fugacity is preferable for volatile chemicals; activity is preferable for non-volatile and ionizable chemicals. The activity approach is a convenient and elegant framework for the exposure assessment of a parent compound

and its degradation products because all metabolic pathways comprise ionizable intermediates (Gasser et al. 2007).

The activity approach enables to describe the behavior of chemicals in non-ideal solutions. However, as the activity refers to chemical species in the water phase, the model only considers the effect of ionic strength in the aqueous phase. The same activity coefficient calculated for water is assumed for solids in a given compartment. This means that feedback effects of dissolved ions on the lipophilicity and on the electrical properties of a solid surface are not considered in the present formulation. Examples of such effects are the salting out of the organic matter in suspended particles and sediments or the neutralization of negative binding sites of suspended solids or of sediments by seawater cations (Turner 2003). Interactions of ionic species with other water solutes are not considered in MAMI. Ionizable chemicals can be emitted as salts or can form complexes in the environment. Complexes may modify speciation and partitioning equilibria in water. The inclusion of complexed species with constant concentration ratios is easily implemented in the model but increases the input data demand.

The new species-specific regressions for the estimation of soil-water partitioning improve the model accuracy for monovalent acids, bases and amphoters. For multivalent organic ionics, there is yet no estimation method available, and if experimental species-specific data are not available, a species-specific simulation cannot be performed. From the list of preregistered REACH substances (ECHA 2009b), several of these multivalent compounds were identified as salts with a valency > ±3. Such compounds may be quickly neutralized by forming complexes in aqueous solutions. Multimedia exposure models, including MAMI, have not been validated for multivalent chemicals, which represent about 18% of the REACH substances (Franco et al. 2010).

The assumption of well mixed compartments and thus of constant concentration within a compartment is particularly problematic for ionic as well as non-ionic surfactants. Multimedia models, including MAMI, do not describe the effects of the enhanced concentrations of surface active substances at the air-water interface, nor the formation of micelles. Current developments, particularly on perfluorinated surfactants, are addressing the influence of surface accumulation on transport mechanisms at the water-air interface (Canadian Environmental Network 2009).

The limits of exposure models based on single parameter (usually K_{OW}) linear free energy relationships (SP-LFERs), like MAMI, are widely recognized. The octanol-water partition coefficient is often not sufficient to describe all interactions affecting the environmental partitioning, in particular for polar molecules. To overcome these limitations, one possibility is to replace SP-LFER by polyparametric LFERs based on the Abraham molecular descriptors. In a recent comparative study, Brown and Wania (2009) assessed the differences between the two modeling approaches and concluded

that SP-LFER are sufficient for screening purposes, while PP-LFERs are preferable for higher tier assessments. The additional input data demand is a limitation of PP-LFER models. The performance of PP-LFER models may increase as soon as better methods for estimating the Abraham molecular descriptors will become available. Yet, the applicability of PP-LFERs to ionizable chemicals is questionable because electrical interactions are not directly quantified by any of the Abraham molecular descriptors.

6. Conclusion

The vast but scattered knowledge available on the influence of ionization on the environmental partitioning and fate of ionizable organic chemicals was exploited in the present project to enlarge the applicability domain and to improve the accuracy of exposure models. Existing models, and in particular the ones described in the EU technical guidance documents for environmental exposure assessment, were used as reference. The new models were developed to make best use of the REACH data requirements, without overly increasing the model complexity.

The two major challenges in the prediction of the environmental behaviour of ionizable chemicals, namely the simultaneous occurrence of two or more species and the impact of electrical interactions, were addressed. The influence of speciation, depending on the dissociation constant and on the pH and, to a lesser extent, of ionic strength, can be described by species-specific partitioning models and integrated in multimedia exposure models. The impact of electrical interactions on the partitioning behaviour of organic anions and cations was considered in the new regression models developed for the soil-water partition coefficient and for the *BCF*. The error of the new regression models for monovalent acids, bases and amphoters is similar to the typical error of single parameter linear free energy relationships developed for neutral substances.

The activity approach proved a convenient complement of the fugacity approach for non-volatile neutral and ionizable organics. It provides the thermodynamically exact model framework to describe the behavior of neutral and ionizable substances under environmental conditions, with variable pH and ionic strength. The approach is well suitable for multispecies compounds. The new species-specific and pH-dependent sorption models for the prediction of the solid-water partition coefficient were integrated in a Multimedia Activity Model for Ionics (MAMI). A validation study on three test chemicals confirmed the potential of MAMI to overcome some limitations of existing models.

In the large and diverse REACH chemical space, some subcategories of ionizable organic chemicals, such as multivalent acids, bases, zwitterions and ionic surfactants, fall outside of the applicability domain of the models presented. Considering their relatively high occurrence, they deserve particular attention in future research.

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8. Appendices

I. Franco A, Ferranti A, Davidsen C, Trapp S. 2009. An unexpected challenge: ionizable compounds in the REACH chemical space. *Int J LCA* (commentary, in print).

II. Franco A, Trapp S. 2008. Estimation of the soil-water partition coefficient normalized to organic carbon for ionizable organic chemicals. *Environ Toxicol Chem 27*: 1995-2004.

III. Franco A, Fu W, Trapp S. 2009. Influence of soil pH on the sorption of ionizable chemicals: modeling advances. *Environ Toxicol Chem* 28: 438-464.

IV. Fu W, Franco A, Trapp S. 2009. Methods for estimating the bioconcentration factor of organic electrolytes. *Environ. Toxicol. Chem.* 28: 1372-1379.

V. Trapp S, Franco A, Mackay D. 2010. Finding activity feasible (draft).

VI. Franco A, Trapp S. 2010. A multimedia activity model for ionizable compounds: validation study with 2,4-dichlorophenoxyacetic acid, aniline and trimethoprim. *Environ Toxicol Chem* 29: (DOI: 10.1002/ect.115, in print).

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